(19) Europäisch s Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 216 746 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication of the patent specification: 24.10.90

(51) Int.Cl.⁵: C07D 241/08

(21) Application number: 86870133.5

(22) Date of filing: 22.09.86

(54) Process to prepare 2,5-diketopiperazines.

(30) Priority: 23.09.85 US 778817

(43) Date of publication of application: 01.04.87 Bulletin 87/14

(45) Publication of the grant of the patent: 24.10.90 Bulletin 90/43

(84) Designated Contracting States: AT BE CH DE FR GB IT LI LU NL SE

(56) References cited:
EP-A- 0 181 152
US-A- 4 140 791

CHEMISTRY LETTERS, 1981, pages 185-188, Tokyo, JP; T. OKAWARA et al.: "Convenient syntheses of piperazine-2,5-diones and lactams from halocarboxamides using phase transfer catalysts"

CHIMIE THERAPEUTIQUE, vol. 4, no. 3, 1969, pages 167-173; A. SUT et al.: "N-Monoalcoylation de quelques dérivés des oxo-2 et dioxo-2,5 pipérazines"

(73) Proprietor: Monsanto Company, Patent Department 800 North Lindbergh Boulevard, St. Louis Missouri 63167-7020(US)

(72) Inventor: Miller, William Harold, 1000 Nancy Carol Lane, Glendale Missouri 63122(US)
Inventor: Taylor, William Donald, 12826 Town and Four, St. Louis Missouri 63141(US)

(74) Representative: Lunt, John Cooper et al, Monsanto Europe S.A. Patent Department Avenue de Tervuren 270-272 Letter Box No 1, B-1150 Brussels(BE)

EP 0 216 746 B1

Description

This invention relates to the synthesis of cyclic peptides, and more particularly to a novel method for the synthesis of substituted and unsubstituted 2, 5-diketopiperazines.

2,5-Diketopiperazines are useful as fungicides and as intermediates for the synthesis of other compounds. Thus, for example, Chan et al, U.S. Patent 4 140 791 discloses the use of 1,4-di(2,6-dimethylphenyl)-2,5-diketopiperazine for control of various fungal diseases. Sut et al "N-Monoalkylation of Some 2-Oxo and 2,5-Dioxopiperazines", Chimie Therapeutique, 4 (3), pp. 167–173 (1969), describes the synthesis of a series of 2-oxopiperazine and 2,5-dioxopiperazines which, were found to have analgesic and anesthetic activities.

The copending and coassigned applications of Miller and Taylor, EP Application No. 36 370 131.9 and Miller, Reitz and Pulwer, EP Application No. 36 870 132.7 describe the use of 1,4-disubstituted 2,5-diketopiperazines in a synthesis scheme leading to the preparation of N-phosphonomethylglycine. N-phosphonomethylglycine, known also by its common name, glyphosate, is a highly effective and commercially important phytotoxicant useful in controlling a large variety of weeds. It is applied to the foliage of a very broad spectrum of perennial and annual grasses and broadleaf plants. Industrial uses include control of weeds along roadsides, waterways, transmission lines, storage areas, and other non-agricultural areas. Usually glyphosate is formulated into herbicidal compositions, preferably in water. The aforesaid copending application of Miller, Reitz and Pulwer (EP Application No. 36 370 132.7 describes a method in which an aqueous solution of N-alkyl glyphosate may be prepared without isolation of intermediates by a reaction scheme commencing with N,N'-dialkyl-2,5-diketopiperazine.

Okawara et al, "Convenient Synthesis of Piperazine-2,5-diones and Lactams from Halocarboxamides Using Phase Transfer Catalysts", Chemistry Letters, 1981, pp. 185–189, describes the synthesis of various 1,4-disubstituted-2,5-diketopiperazines by intermolecular condensation of halocarboxamides using a reaction system comprising a mixture of dichloromethane and 50% aqueous sodium hydroxide solution in the presence of a solid phase transfer catalyst. Among the compounds whose synthesis are reported by Okawara et al are 1,4-dibenzylpiperazine-2,5-dione, 1,4-diphenylpiperazine-2,5-dione and 1,4-diphenyl-3,6-dimethylpiperazine2,5-dione. The reference does not report any use for the products synthesized.

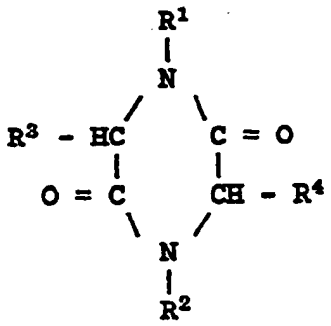
Cavicchioni et al, "Base Promoted Reactions of α-Halogeno-alkylanilides," Chem. Soc. Perkin Trans. J, pp. 2969-2972 (1982), reports the preparation of both N, N'-dialkylpiperazines and 2-amino-2-haloalkyloxazolidones by intermolecular condensations of the same reactants used in the synthesis described by Okawara. Cavicchioni et al do not give much detail on the reaction system utilized but apparently employed a polar organic solvent system rather than a two-phase system comprising a phase transfer catalyst.

Wong et al U.S. Patent 4 400 330 describes the preparation of bis-phosphonomethyl-2,5-diketopiperazine by phosphonomethylation of 2,5-diketopiperazine, followed by hydrolysis of the bis-phosphonomethyl-2,5-diketopiperazine to produce glyphosate. In the phosphonomethylation, formaldehyde and glacial acetic acid are added to 2,5-diketopiperazine io produce a suspension which is refluxed. Thereafter, phosphorus trichloride is added to the reaction mixture which is then maintained at reflux until all hydrogen chloride by-product has been driven off. After additional refluxing of the reaction slurry, the product is dried in vacuo, dissolved in water, and treated sequentially with caustic solution and mineral acid to effect hydrolysis and produce glyphosate.

SUMMARY OF THE INVENTION

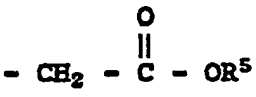
Among the several objects of the present invention may be noted the provision of a novel and improved method for the synthesis of substituted or unsubstituted 2,5-diketopiperazines; the provision of such a method which affords both high productivity and high yield; the provision of such a method which can be economically implemented; and in particular provision of such a method which does not require the use of a phase transfer catalyst.

These and other objects are achieved by a process for the preparation of a substituted or unsubstituted 2,5-diketopiperazine represented by the formula:



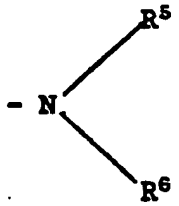
where R^3 and R^4 are independently selected from the group consisting of hydrogen, alkyl and aryl, and R^1 and R^2 are independently selected from the group consisting of hydrogen, alkyl having between 1 and about 12 carbon atoms, arylmethyl, aryl,

and

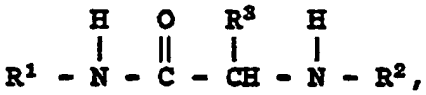


where Y is selected from the group consisting of

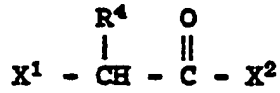
- $-OR^5$,
- $-SR^5$, and



and R^5 and R^6 are independently selected from the group consisting of alkyl having between 1 and about 6 carbon atoms; the process comprising bringing together under reaction conditions a substituted or unsubstituted glycinamide represented by the formula:



where R^1, R^2 and R^3 are as defined above, and a haloacetyl halide represented by the formula:

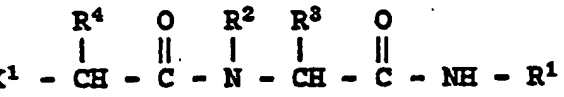


where X^1 and X^2 are halogen and R^4 is as defined above, and in the presence of a base forming said substituted or unsubstituted 2,5-diketopiperazine.

Other objects and features will be in part apparent and in part pointed out hereafter.

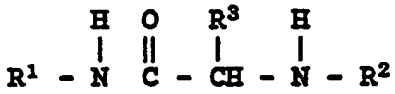
DESCRIPTION OF THE PREFERRED EMBODIMENT

In accordance with the invention, it has been found that substituted and unsubstituted 2,5-diketopiperazines can be synth sized in high yield and at high productivity by reaction of a substituted or unsubstituted glycinamide with a haloacetyl halide. Although applicants do not wish to be bound by any particular theory, it is believed that a linear intermediate is formed by condensation of the glycinamide and haloacetyl halide, which can be represented by the following formula:

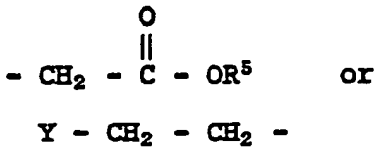


where X^1, R^1, R^2, R^3 and R^4 are as defined above. It is believed that the intermediate undergoes cyclization in the presence of strong base to form the 2,5-diketopiperazine. The process of the invention is economical to implement and is particularly advantageous in avoiding the need for a phase transfer catalyst to promote the progress of the formation of the 2,5-diketopiperazine.

Generally, the glycinamide can be represented by the formula:

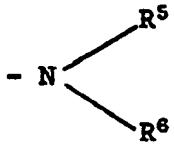


where R^1, R^2, and R^3 are as defined above. Thus, where R^1 and/or R^2 is an alkyl group, it may typically comprise methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, n-pentyl, n-hexyl, 2-ethylhexyl, n-octyl, n-decyl or n-dodecyl. Where R^1 and/or R^2 is an arylmethyl group, it is typically benzyl, but may also be a substituted benzyl such as nitrobenzyl or sulfonated benzyl. Similarly, where R^1 and/or R^2 is aryl, it is typically phenyl, but may alternatively be nitrophenyl, sulfonated phenyl, hydroxyphenyl, or carboxyphenyl. As noted, R^1 or R^2 may also comprise



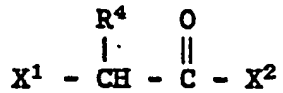
where Y is selected from among

– OR^5,
– SR^5, and



where R^5 and R^6 are independently selected from among alkyl groups having between about 1 and about 6 carbon atoms and aryl. Thus, typically, R^5 and/or R^6 may comprise methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, or n-hexyl.

The haloacetyl halide reactant corresponds to the formula:



where X^1 and X^2 are both halogen, and R^4 is as defined above. Among the specific substituents which can typically comprise R^3 or R^4 are ethyl, propyl, n-butyl, n-hexyl and phenyl. Preferably, however, R^3 and R^4 comprise hydrogen, and th haloacetyl halide reactant corresponds to the f rmula:

$$X^{1'} - CH_2 - \overset{O}{\overset{\|}{C}} - X^{2'}$$

where $X^{1'}$ and $X^{2'}$ are independently selected from among chlorine and bromine. Preferably, the haloacetyl halide is chloracetyl chloride.

To carry out the process, the N,N'-disubstituted glycinamide reactant is preferably dissolved in an organic solvent and the haloacetyl halide added slowly, for example drop-wise, to the solution. The solvent utilized comprises an organic solvent which is inert to the haloacetyl halide under the reaction conditions. Most preferably, toluene or xylene is utilized as the reaction solvent.

As noted above, the formation of the 2,5-diketopiperazine must be carried out in the presence of a hydrogen halide scavenger. Although any number of hydrogen halide scavengers are known to those skilled in the art, it is preferred to use a non-nucleophilic base, which is incorporated in the solution containing the substituted or unsubstituted glycinamide prior to addition of the haloacetyl halide. The non-nucleophilic base serves as a hydrogen halide scavenger and in some cases may promote the initial condensation between the substituted or unsubstituted glycinamide and the haloacetyl halide. In general, when a non-nucleophilic base is used, a stronger base is subsequently added to form the desired product.

The initial condensation proceeds rapidly, and substantially quantitatively. Accordingly, the amount of haloacetyl halide charged to the reaction is conveniently and preferably equivalent to the initial glycinamide charge. The non-nucleophilic base is preferably an organic amine such as, for example, triethylamine or pyridine. Alternatively, an excess of the substituted or unsubstituted glycinamide reactant itself may be used as the non-nucleophilic base. The amount of base charged to the reaction (or in the case of glycinamide, the excess over that to be reacted with the haloacetyl halide) should be at least about one equivalent per equivalent of haloacetyl halide charged.

Prior to and during the addition of haloacetyl halide, the system is preferably maintained at a temperature not greater than room temperature, more preferably 0-15°C, typically by use of an ice bath or refrigeration. After addition of the haloacetyl halide is complete, the temperature is allowed to rise to room temperature or somewhat above. At this point, a minor proportion of phase transfer catalyst optionally may be added to the reaction system, for example, between about 0.1% and about 3% by weight based on the amount of substituted or unsubstituted glicinamide in the charge. Preferably, however, the phase transfer catalyst is entirely omitted.

Thereafter caustic, preferably either NaOH or KOH, is added to the mixture to effect cyclization.

Either powdered caustic or a 50% or greater aqueous solution may be used. Where powdered caustic is used, between about 1 and about 2 moles should be charged per mole of product. Where 50% caustic solution is used, at least about 4 moles should be charged. To complete the cyclization, the system is heated to a temperature between about 50° and about 150°C, preferably between about 75° and about 90°C, typically for one to three hours.

The product 2, 5-diketopiperazine is conveniently recovered by simple phase separation, drying the organic phase (for example, over anhydrous magnesium sulfate) and stripping the solvent. Alternatively, and especially where an N, N', substituted 2, 5-diketopiperazine is to be used in the synthesis of glyphosate or glyphosate precursors, the product can be subjected to further reaction after removal of the solvent. Thus, for example, the product may be converted to an N-substituted glycine or N-substituted glyphosate in accordance with the methods described in the copending applications of Miller and taylor, EP Applications No. 86870131.9 or Miller, Reitz and Pulwer, EP Application No. 86870132.7.

Although particularly useful for the preparation of symmetrical 1,4-dialkyl-2,5-diketopiperazines for use in glyphosate synthesis, the process of the invention also affords an advantageous method for the preparation of specific asymmetric 1- and/or 4-substituted 2,5-diketopiperazines. Such can be prepared by selecting a glycinamide which initially contains the particular R^1 and R^2 substituents desired. Condensation of this glycinamide with haloacetyl halide and cyclization in the presence of alkali provides high conversion to the desired species. By contrast, synthesis from two different α-halocarboxamides, using the method of Okawara or Cavicchioni, produces a mixture of the desired asymmetric product with two by-products, one in which both nitrogens are substituted with R^1, and another in which both nitrogens are substituted with R^2. Furthermore, the present method also allows for the specific preparation of asymmetrically 3- and/or 4 substituted 2,5-diketopiperazines, which by prior art methods would provide unwanted mixtures of products as described above.

The following examples illustrate the invention.

Example 1

Toluene (50 ml), N,N'-diisopropylglycinamide (3.96 g; 0.025 mol) and triethylamine (2.53 g; 0.025 mol) were charged to a 100 ml round bottom flask that was equipped with a magnetic stir bar and an addition funnel. The flask was cooled to 0-5°C in an ice bath and chloracetyl chloride (2.83 g; 0.025 mol) was added dropwise via the addition funnel. The mixture was then allowed to warm to room temperature and was

stirred for about 30 minutes. The mixture was then filtered. The filtrates were combined and charged to a 500 ml Morton flask equipped with a thermometer, condenser and mechanical stirrer. Powdered sodium hydroxide (2.0 g; 0.050 mol) was charged to the flask and the reaction mixture was vigorously stirred and heated to 80°C for one hour. The reaction mixture was then filtered and solvent removed under reduced pressure to give 4.68 g (94.4% yield) of 1,4-diisopropylpiperazine-2,5-dione as an off-white solid. The solids were crystallized from ethanol to give a white, crystalline solid having a melting point of 177-180°C. Analytical results on the product were as follows:
^{1}H NMR ($CDCl_3$, TMS, 90 MHZ), δ 4.77 (Septet, J=7Hz,2H), 3.83 (S, 4H), 1.15 (d,J=7Hz12H), $C_{10}H_{18}N_2O_2$ calc., C 60.58, H 9.15, N 14.13 (198.27) found 60.49, 9.16, 14.10 MS, m/e = 198 (parent)

Example 2

The compound N,N'-diisopropylglycinamide (15.6 g; 0.1 mole), methylene chloride (50 ml), and a 50% by weight sodium hydroxide solution (80 g) were charged to a flask and cooled in an ice bath. Chloracetyl chloride (11.2 g; 0.1 mole) was thereafter added dropwise and the reaction mixture was then allowed to come to room temperature. At this point, benzyltriethylammonium chloride (0.45 g) was added and the reaction mixture was stirred for 1.5 hours. The phases were separated, the organic phase was dried (over calcium chloride), and the volatiles were removed to leave 15.8 g (79.6% yield) of 1,4-diisopropylpiperazine-2,5-dione.

Example 3

The compound N,N'-diisopropylglycinamide (7.91 g; 0.05 mole), toluene (70 ml), and triethylamine (5.06 g; 0.05 mole) were charged to a 500 ml Morton flask equipped with a mechanical stirrer, addition funnel and thermometer. The resulting mixture was cooled in an ice bath and chloracetyl chloride (5.65 g; 0.05 mole) was slowly added dropwise via the addition funnel. After addition of the chloractyl chloride was completed, the flask was allowed to warm to room temperature and stirred for one hour. The flask was then charged with six equivalents (12.0 g) of solid powdered sodium hydroxide. The addition funnel was replaced with a condenser, and the mixture was vigorously stirred and heated to 70°C. After the mixture had been stirred and heated for 1.5 hour, it was cooled and filtered. The collected solids were washed with methylene chloride. The filtrates and washings were combined and the solvent was removed under reduced pressure to give 8.99 g (90.7% of theoretical yield) of 1,4-diisopropylpiperazine-2,5-dione as a yellow-white solid.

Example 4

The compound N,N'-diisopropylglycinamide (7,91 g; 0.05 mole), triethylamine (5.06 g; 0.05 mole), and toluene (70 ml) were charged to a 500 ml Morton flask equipped with a mechanical stirrer and addition funnel. The mixture was cooled in an ice bath and chloracetyl chloride was slowly added dropwise to the stirred solution. Upon completion of the addition of the chloracetyl chloride, the ice bath was removed and the flask allowed to warm to room temperature and stirred for about 30 minutes. A precipitate was observed in the reaction flask. The flask was then charged with 50% by weight sodium hydroxide solution (24 g) and heated to 70°C with vigorous stirring. After the mixture was heated and stirred for one hour, a sample was taken and analyzed by gas chromatography. The results showed 96.3% (area %) of N,N'-diisopropyl-2,5-diketopiperazine with virtually no remaining glycinamide (less then 2.7%).
The reaction mixture was worked up by adding methylene chloride (50 ml), separating the caustic layer, and washing the caustic layer with an additional aliquot of methylene chloride (1 x 25 ml). The organic layers were combined, washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure to give 8.82 g (89%) yield of a pale, yellow white solid.

Example 5

Toluene (70 ml), N-isopropyl-2-benzylaminoacetamide (4.12, 0.02 mole) and triethylamine (2.02 g, 0.02 mole) were charged to a 100 ml round bottom flask equipped with a magnetic stir bar and an addition funnel. The flask was cooled to 0-5°C in an ice bath and chloracetyl chloride (2.26 g, 0.02 mole) was added dropwise via the addition funnel. The mixture was then allowed to warm to room temperature and was stirred for 30 minutes. The mixture was then filtered. The filtrates were charged to a 500 ml Morton flask equipped with a thermometer, condenser and mechanical stirrer. Powdered sodium hydroxide (4.0 g, 0.10 mole) was charged to the flask and the mixture was vigorously stirred and heated to 70°C for one hour. The mixture was filtered and solvent removed under reduced pressure to give 4.57 g (92.8%) of a tan solid. The solids were recrystallized from toluene to give a white, crystalline solid, melting point 106.5 - 107.5°C, identified as 1-isopropyl-4-benzylpiperazine-2,5-dione from the following analytical data:
NMR ($CDCl_3$, TMS, 90 MHz) δ 7.30 (s, 5H), 4.78 (septet, J=7Hz, IH), 4.60 (s, 2H), 3.90 (s, 2H), 3.80 (s, 2H), 1.18 (d J=7Hz, 6H). Mass spectroscopy showed parent ion, m/e 246 and elemental analysis gave the following results:

	CALCULATED	FOUND
C	68.27%	68.33%
H	7.37	7.38
N	11.37	11.33

Example 6

Toluene (75 ml), N,N'-dibenzylglycinamide (6.36 g, 0.025 mole) and triethylamine (2.53 g, 0.025 mole) were charged to a 100 ml round bottom flask that was equipped with a magnetic stir bar and an addition funnel. The flask was cooled to 0-5°C in an ice bath and chloracetyl chloride (2.83 g, 0.025 mole) was added dropwise via the addition funnel. The mixture was then allowed to warm to room temperature and was stirred for 30 minutes. The mixture was then filtered. The filtrates were charged to a 500 ml Morton flask equipped with a thermometer, condenser and mechanical stirrer. Powdered sodium hydroxide (5.0 g, 0.125 mole) was charged to the flask and the mixture was vigorously stirred and heated to 70°C for one hour. The mixture was then filtered and solvent removed under reduced pressure to give 6.69 g (91%) of a brown solid. The solids were recrystallized from chloroform to give a white, crystalline solid, melting point 173-174.5°C, identified as 1,4-dibenzylpiperazine-2,5-dione from the following analytical data:
NMR ($CDCl_3$, TMS 90 MHz) δ 7.25 (s, 10H), 4.54 (s, 4H), 3.85 (s, 4H). Mass spectroscopy showed parent ion, m/e 294, and elemental analysis gave the following results:

	CALCULATED	FOUND
C	73.45%	73.53%
H	6.16	6.18
N	9.52	9.50

Example 7

Toluene (50 ml), N,N'-diisopropylglycinamide (3.95 g, 0.025 mole) and triethylamine (2.53 g, 0.025 mole) were charged into a 100 ml round bottom flask that was equipped with a magnetic stir bar and an addition funnel. The flask was cooled to 0-5°C in an ice bath and 2-chloropropionyl chloride (3.17 g, 0.025 mole) was added dropwise via the addition funnel. The mixture was then allowed to warm to room temperature and was stirred for 30 minutes. The mixture was then filtered. The filtrates were combined and charged to a 500 ml Morton flask equipped with a thermometer, condenser and mechanical stirrer. Powdered sodium hydroxide (2.0 g, 0.05 mole) was charged to the flask and the mixture was vigorously stirred and heated to 80°C for one hour. A sample of the mixture was analyzed by NMR and showed incomplete conversion to product. Fresh sodium hydroxide (2.0 g, 0.05 mole) was charged into the flask and heating and stirring was continued for an additional hour. NMR then showed complete conversion. The mixture was then filtered and solvent removed under reduced pressure to give 4.64 g, (87%) of a pale yellow-white solid. The solids were recrystallized from toluene to give a white solid, mp 160-163°C, identified as 1,4-diisopropyl3-methylpiperazine-2,5-dione from the following analytical data:
NMR ($CDCl_3$, TMS, 360 MHz) δ 4.72 (septet, J=7, 1H), 4.52 (septet, J=7Hz, 1H), 4.00 (q, J=7Hz, 1H), 3.79 (s, 2H), 1.43 (d, J=7Hz, 3H), 1.24 (d, J=7Hz, 3H), 1.20 (d, J=7Hz, 3H), 1.14 (d, J=7Hz, 3H), 1.11 (d, J=7Hz, 3H). Mass spectroscopy showed parent ion, m/e 212 and elemental analysis gave the following results:

	CALCULATED	FOUND
C	62.23%	62.01%
H	9.50	9.58
N	13.20	13.14

Example 8

Toluene (50 ml), N-isopropyl-2-benzylaminopropionamide (5.51 g, 0.025 mole) and triethylamine (2.53 g, 0.025 mole) were charged to a 100 ml round-bottom flask equipped with a magnetic stir bar and an addition funnel. The flask was cooled to 0-5°C in an ice bath and 2-chloro-2-phenylacetyl chloride (98%) (4.98 g, 0.025 m le) was added dropwise via th addition funnel. The flask was allowed to warm to room temperature and stirred for about 30 minutes. The mixture was then filtered. The filtrates were charged to a 500 ml Morton flask equipped with a thermometer, condenser and mechanical stirrer. Powdered sodium hydroxide (2.0 g, 0.05 mole) was charged to the flask and the mixture was vigorously stirred at 70-80°C for two hours. The mixture was then filtered and solvent removed under reduced pressure to give an orange-yellow oil, which was purified by chromatography on silica gel. Elution with 10% ethyl acetate-hexane gave 0.39 g (4.6%) of a yellow oil, identified as 1-isopropyl-3-methyl-4-benzyl-6-phenylpiperazine-2,5-dione. Analytical data are presented below:
NMR ($CDCl_3$), TMS, 360 (MHz) δ 7.34 (m, 10H), 4.97 (septet, J=7Hz, 1H), 4.54 (s, 1H), 3.77 (m, 2H), 3.54 (d, J=13Hz, 1H), 1.46 (d, J=7Hz, 3H), 1.42 (d, J=7Hz, 3H), 1.39 (d, J=7Hz, 3H); MS, m/e 336, 245, 132, 91. Anal. calculated for $C_{21}H_{24}N_2O_2$:

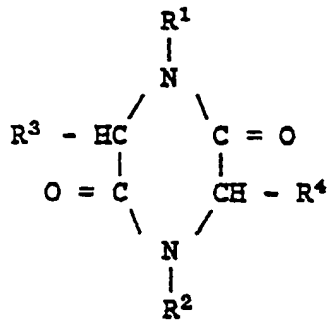
	CALCULATED	FOUND
C	74.97	74.77
H	7.19	7.23
N	8.33	8.26

In view of the above, it will be seen that the several objects of the invention are achieved and other advantageous results attained.

As various changes could be made in the above methods without departing from the scope of the invention, it is intended that all matter contained in the above description or shown in the accompanying drawings shall be interpreted as illustrative and not in a limiting sense.

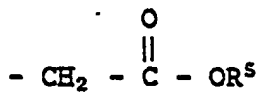
Claims

1. A process for the preparation of a substituted or unsubstituted 2,5-diketopiperazine represented by the formula :



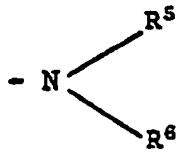
where R^3 and R^4 are independently selected from hydrogen, alkyl and phenyl, and R^1 and R^2 are independently selected fromnitrobenzyl and sulfonated hydrogen, C1–C12 alkyl, benzyl and phenyl, nitrophenyl, sulfonated phenyl, hydrogenphenyl or carboxyphenyl,

$$Y - CH_2 - CH_2 - \quad \text{and}$$

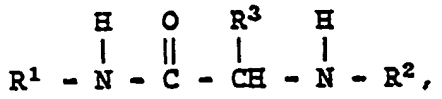


where Y is selected from the group consisting of

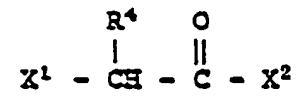
– OR^5,
– SR^5, and



and R^5 and R^6 are independently selected from the group consisting of C1–C6 alkyl; the process comprising reacting a substituted or unsubstituted glycinamide represented by the formula :



where R^1, R^2 and R^3 are as defined above, with a haloacetyl halide represented by th formula :



where X^1 and X^2 are halogen and R^4 is as defined above, and in the presence of a reagent which serves as an hydrogen halide scavenger and a base.

2. A process as set forth in Claim 1 wherein R^1 and R^2 are the same.

3. A process as set forth in Claim 2 wherein R1 and R^2 are C1–C12 alkyl.

4. A process as set forth in Claim 3 wherein R^1 and R^2 are isopropyl.

5. A process as set forth in Claim 2 wherein R^1 and R^2 are benzyl.

6. A process according to any of Claims 1 to 5 wherein the reagent is caustic and selected from sodium hydroxide and potassium hydroxide.

7. A process according to any of Claims 1 to 5 wherein the substituted or unsubstituted glycinamide and the haloacetyl halide are reacted in the presence of an hydrogen halide scavenger and thereafter of a stronger base which is subsequently added to the reaction mixture.

8. A process as set forth in Claim 7 wherein the hydrogen halide scavenger is a non-nucleophilic base.

9. A process as set forth in Claim 8 wherein said non-nucleophilic base comprises a non-nucleophilic organic amine.

10. A process as set forth in Claim 9 wherein said non-nucleophilic organic amine is selected from the group consisting af triethylamine and pyridine.

11. A process as set forth in Claim 9 wherein the non-nucleophilic organic amine is a stoichiometric excess of the substituted or unsubstituted glycinamide with respect to the amount of haloacetyl halide present.

12. A process as set forth in Claim 9 wherein the haloacetyl halide is added slowly to a solution comprising said substituted or unsubstituted glycinamide and said non-nucleophilic organic amine, and thereafter, caustic selected from the group consisting of sodium hydroxide and potassium hydroxide is added to the solution to form the diketopiperazine.

13. A process as set forth in Claim 12 wherein said caustic comprises a powdered alkali metal hydroxide and is added in a proportion of between about 1 and about 2 moles per mole of haloacetyl halide charged.

14. A process as set forth in CLaim 12 wherein said caustic comprises an aqueous solution containing at least about 50% by weight of an alkali metal hydroxide and is added in a proportion of at least about 4 moles per mole of haloacetyl halide.

15. A process as set forth in Claim 12 wherein saud solvent comprises an organic solvent which is not reactive with haloacetyl halide.

16. A process as set forth in Claim 15 wherein said solvent is selected from the group consisting of toluene and xylene.

17. A process as set forth in Claim 12 wherein the diketopiperazine is formed at a temperature of between about 50° and about 150°C.

18. A process as set forth in Claim 1 wherein said haloacetyl halide is represented by the formula :

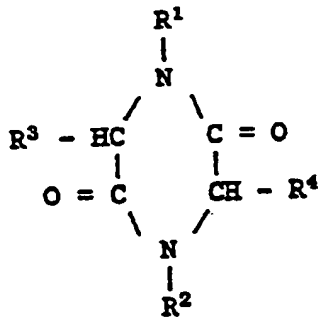
$X^{1'}$ -CH_2-CO-$X^{2'}$

wherein $X^{1'}$ and $X^{2'}$ are independently selected from the group consisting of chlorine and bromine.

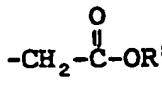
19. A process as set forth in Claim 18 wherein said haloacetyl halide is chloracetyl chloride.
20. A process as set forth in Claim 19 wherein R^1 and R^2 are isopropyl.
21. A process as set forth in Claim 19 wherein R^1 and R^2 are benzyl.

Patentansprüche

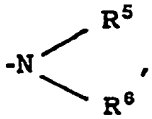
1. Verfahren zur Herstellung eines substituierten oder unsubstituierten 2,5-Diketopiperazons der Formel



worin R^3 und R^4 unabhängig ausgewählt sind aus Wasserstoff, Alkyl und Phenyl und R^1 und R^2 unabhängig ausgewählt sind aus Wasserstoff, C_1–C_{12}-Alkyl, Benzyl, Nitrobenzyl und sulfoniertem Benzyl, Phenyl, Nitrophenyl, sulfoniertem Phenyl, Hydroxyphenyl oder Carboxyphenyl, Y–CH_2–CH_2– und

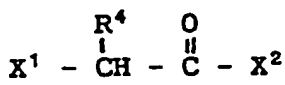


wobei Y ausgewählt ist aus der Gruppe bestehend aus –OR^5, –SR^5 und



wobei R^5 und R^6 unabhängig ausgewählt sind aus C_1–C_6-Alkyl, welches Verfahren das Umsetzen eines substituierten Glycinamids der Formel

worin R^1, R^2 und R^3 wie oben definiert sind, mit einem Halogenacetylhalogenid der Formel



worin X^1 und X^2 Halogen bedeuten und R^4 wie oben definiert ist, und in Anwesenheit eines Reagens, das als Halogenwasserstoffänger und als Base dient, umfaßt.

2. Verfahren nach Anspruch 1, worin R^1 und R^2 gleich sind.
3. Verfahren nach Anspruch 2, worin R^1 und R^2 C_1–C_{12}-Alkyl sind.
4. Verfahren nach Anspruch 3, worin R^1 und R^2 Isopropyl sind.
5. Verfahren nach Anspruch 2, worin R^1 und R^2 Benzyl sind.
6. Verfahren nach einem der Ansprüche 1 bis 5, worin das Reagens kaustisch ist und ausgewählt ist aus Natriumhydroxid und Kaliumhydroxid.
7. Verfahren nach einem der Ansprüche 1 bis 5, worin das substituierte oder unsubstituierte Glycinamid und das Halogenacetylhalogenid in Anwesenheit eines Halog nwasserstoffängers und dann einer stärkeren Base, die der Reakti nsmischung anschließend zugesetzt wird, umgesetzt werden.

8. Verfahren nach Anspruch 7, worin der Halogenwasserstoffänger eine nicht-nukleophile Base ist.

9. Verfahren nach Anspruch 8, worin die nicht-nukleophile Base ein nicht-nukleophiles organisches Amin umfaßt.

10. Verfahren nach Anspruch 9, worin das nicht-nukleophile organische Amin ausgewählt ist aus der Gruppe bestehend aus Triäthylamin und Pyridin.

11. Verfahren nach Anspruch 9, worin das nicht-nukleophile organische Amin ein stöchiometrischer Überschuß des substituierten oder unsubstituierten Glycinamids in bezug auf die Menge des vorhandenen Halogenacetylhalogenids ist.

12. Verfahren nach Anspruch 9, worin das Halogenacetylhalogenid langsam einer Lösung zugesetzt wird, die das substituierte oder unsubstituierte Glycinamid und das nicht-nukleophile organische Amin umfaßt und danach kaustisches Material ausgewählt aus der Gruppe bestehend aus Natriumhydroxid und Kaliumhydroxid der Lösung zur Bildung des Diketopiperazins zugesetzt wird.

13. Verfahren nach Anspruch 12, worin das kaustische Material ein pulverförmiges Alkalimetallhydroxid umfaßt und in einer Menge von etwa 1 bis etwa 2 Molen pro Mol eingesetztem Halogenacetylhalogenid zugesetzt wird.

14. Verfahren nach Anspruch 12, worin das kaustische Material eine wässerige Lösung umfaßt, die mindestens etwa 50 Gew.% eines Alkalimetallhydroxids enthält, und in einer Menge von mindestens etwa 4 Molen pro Mol Halogenacetylhalogenid zugesetzt wird.

15. Verfahren nach Anspruch 12, worin das Lösungsmittel ein organisches Lösungsmittel umfaßt, das mit Halogenacetylhalogenid nicht reaktionsfähig ist.

16. Verfahren nach Anspruch 15, worin das Lösungsmittel ausgewählt ist aus der Gruppe bestehend aus Toluol und Xylol.

17. Verfahren nach Anspruch 12, worin das Diketopiperazin bei einer Temperatur von etwa 50 bis etwa 150°C gebildet wird.

18. Verfahren nach Anspruch 1, worin das Halogenacetylhalogenid die Formel $X^{1'}–CH^2–CO–X^{2'}$ aufweist, worin $X^{1'}$ und $X^{2'}$ unabhängig ausgewählt sind aus der Gruppe bestehend aus Chlor und Brom.

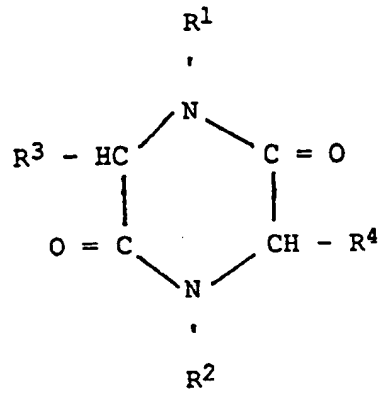
19. Verfahren nach Anspruch 18, worin das Halogenacetylhalogenid Chloracetylchlorid ist.

20. Verfahren nach Anspruch 19, worin R^1 und R^2 Isopropyl sind.

21. Verfahren nach Anspruch 19, worin R^1 und R^2 Benzyl sind.

Revendications

1. Procédé de préparation d'une 2,5-dicétopipérazine substituée ou non substituée répondant à la formule:



dans laquelle R^3 et R^4 sont choisis indépendamment parmi un atome d'hydrogène, un groupe alkyle et phényle et R^1 et R^2 sont choisis indépendamment parmi un atome d'hydrogène, un groupe alkyle en C^1 à C^{12}, un groupe benzyle, nitrobenzyle et benzyle sulfoné, phényle, nitrophényle, phényle sulfoné, hydroxyphényle ou carboxyphényle,

$$Y - CH_2 - CH_2 - \qquad \text{et}$$

$$- CH_2 - \overset{\overset{O}{\|}}{C} - OR^5$$

où Y est choisi parmi
$-OR^5$,
$-SR^5$, et

$$-N\begin{matrix}\nearrow R^5 \\ \searrow R^6\end{matrix}$$

et R^5 et R^6 sont choisis indépendamment parmi les groupes alkyle en C_1 à C_6, le procédé comprenant le fait de faire réagir un glycinamide substitué ou non substitué répondant à la formule:

$$R^1 - N - \overset{\overset{O}{\|}}{C} - \overset{\overset{R^3}{|}}{CH} - N - R^2,$$
$$\qquad\qquad\qquad\quad H \qquad\qquad\quad H$$

dans laquelle R^1, R^2 et R^3 sont tels que définis ci-dessus, avec un halogénure d'haloacétyle répondant à la formule:

$$X^1 - \overset{\overset{R^4}{|}}{CH} - \overset{\overset{O}{\|}}{C} - X^2$$

dans laquelle X^1 et X^2 sont des atomes d'halogène et R^4 est tel que défini ci-dessus, et en présence d'un réactif qui sert de composé fixant l'halogénure d'hydrogène et d'une base.

2. Procédé selon la revendication 1, dans lequel R^1 et R^2 sont identiques.

3. Procédé selon la revendication 2, dans lequel R^1 et R^2 sont des groupez alkyle en C_1 à C_{12}.

4. Procédé selon la revendication 3, dans lequel R^1 et R^2 sont des groupes isopropyle.

5. Procédé selon la revendication 2, dans lequel R^1 et R^2 sont des groupes benzyle.

6. Procédé selon l'une quelconque des revendications 1 à 5, dans lequel le réactif est un alcali caustique et est choisi parmi l'hydroxyde de sodium et l'hydroxyde de potassium.

7. Procédé selon l'une quelconque des revendications 1 à 5, dans lequel le glycinamide substitué ou non substitué et l'halogénure d'haloacétyle sont mis à réagir en présence d'un composé fixant l'halogénure d'hydrogène, puis d'une base plus forte qui est ensuite ajoutée au mélange réactionnel.

8. Procédé selon la revendication 7, dans lequel le composé fixant l'halogénure d'hydrogène est une base non nucléophile.

9. Procédé selon la revendication 8, dans lequel cette base non nucléophile comprend une amine organique non nucléophile.

10. Procédé selon la revendication 9, dans lequel cette amine organique non nucléophile est choisie parmi la triéthylamine et la pyridine.

11. Procédé selon la revendication 9, dans lequel l'amine organique non nucléophile est un excès stoechiométrique du glycinamide substitué ou non substitué par rapport à la quantité d'halogénure d'haloacétyle présente.

12. Procédé selon la revendication 9, dans lequel l'halogénure d'halocétyle est ajouté lentement à une solution comprenant ce glycinamide substitué ou non substitué et cette amine organique non nucléophile, puis un alcali caustique choisi parmi l'hydroxyde de sodium et l'hydroxyde de potassium est ajouté à la solution pour former la dicétopipérazine.

13. Procédé selon la revendication 12, dans lequel cet alcali caustique comprend un hydroxyde de métal alcalin pulvérisé et est ajouté dans une proportion comprise entre environ 1 et environ 2 moles par mole d'halogénure d'haloacétyle introduite.

14. Procédé selon la revendication 12, dans lequel cet alcali caustique comprend une solution aqueuse contenant au moins environ 50% en poids d'un hydroxyde de métal alcalin et est ajouté dans une proportion d'au moins environ 4 moles par mole d'halogénure d'haloacétyle.

15. Procédé selon la revendication 12, dans lequel ce solvant comprend un solvant organique qui n'est pas réactif avec l'halogénure d'haloacétyle.

16. Procédé selon la revendication 15, dans lequel ce solvant est choisi parmi le toluène et le xylène.

17. Procédé selon la revendication 12, dans lequel la dicétopipérazine est formée à une température comprise entre environ 50° et environ 150°C.

18. Procédé selon la revendication 1, dans lequel cet halogénure d'haloacétyle est représenté par la formule:

$X^{1'}\text{-}CH_2\text{-}CO\text{-}X^{2'}$

dans laquelle $X^{1'}$ et $X^{2'}$ sont choisis indépendamment parmi les atomes de chlore et de brome.

19. Procédé selon la revendication 18, dans lequel cet halogénure d'haloacétyle est le chlorure de chloracétyle.

20. Procédé selon la revendication 19, dans lequel R^1 et R^2 sont des groupes isopropyle.

21. Procédé selon la revendication 19, dans lequel R^1 et R^2 sont des groupes benzyle.